Remarks

Claims 1-9 are pending in the subject application. Applicants gratefully acknowledge the Examiner's withdrawal of the finality of the rejections in the Office Action dated August 19, 2002. By this Amendment, Applicants have amended claims 1 and 8 and canceled claim 7. Support for the amendments can be found throughout the subject specification and in the claims as originally filed. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 1-6, 8, and 9 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Applicants acknowledge the Examiner's comments in the instant Action regarding the preferred format for arrangement of a specification. The subject specification does include a title, a background of the invention (including a field of invention), a brief summary of the invention, a (detailed) description of the invention, sequence listing, claims, abstract of the disclosure, and drawings, in that order. Thus, Applicants respectfully assert that the subject specification complies with the suggested arrangement, except for the location of the sequence listing. If the Examiner prefers that the sequence listing be at the very end of the specification, Applicants will be happy to amend the specification to comply.

Claim 1 is objected to in regard to the use of the acronym VEGF. Claim 1 has been amended in accordance with the Examiner's helpful suggestion, *i.e.*, to recite "vascular endothelial growth factor" with the acronym "VEGF" in parentheses. Accordingly, reconsideration and withdrawal of the objection is respectfully requested.

Claims 1-9 are rejected under 35 USC §112, first paragraph, as nonenabled by the subject specification. The Examiner asserts that the subject specification does not enable treatment of any vascular disorder other than intimal hyperplasia in any species other than a rabbit using any VEGF receptor agonist other than VEGF. Applicants respectfully traverse.

The Examiner asserts under this rejection that "there is no nexus between any site of injury and any hyperplastic site" and that the claims read upon treatment of intimal hyperplasia by "administration of nucleic acids at periadventitial sites distal to the site of disease." The Examiner further states that the claims "do not limit the site of delivery of nucleic acids, relative to the site to be treated" and, therefore, asserts that the claims embrace "systemic intravascular delivery" of the

nucleic acid compositions. Applicants respectfully disagree with the Examiner's characterization and note that claim 1 specifically recites that the claimed method relies on "periadventitial administration" of the therapeutic agent to a blood vessel. The term "periadventitial" is generally understood in the art to mean around or surrounding the outer coat of a blood vessel or other structure. Thus, Applicants respectfully assert that the claimed method does not encompass systemic intravascular delivery of nucleic acids and that it would be understood that there is a nexus between the site of injury and the site of administration of treatment. However, in order to lend greater clarity, Applicants have amended claim 1 to recite that the therapeutic agent is administered at a site where intimal hyperplasia is present or may occur in the blood vessel.

Also under this rejection the Examiner asserts that the subject specification does not teach prevention of intimal hyperplasia, or reversal of existing hyperplasia. Applicants respectfully assert that the claimed methods are enabled for treatment of intimal hyperplasia that may be present in a blood vessel and are enabled for prevention of intimal hyperplasia from occurring at a site where intimal hyperplasia may occur in a blood vessel. However, in an effort to expedite prosecution of the subject application to completion, Applicants have amended claim 1 to read as "A method for treating or inhibiting intimal hyperplasia of a blood vessel . . .." The Examiner acknowledges at page 8 of the instant Office Action that the claimed method is enabled for inhibiting intimal hyperplasia. In addition, as noted above, Applicants have amended claim 1 to recite that the agent is administered at a site where intimal hyperplasia is present or may occur in the blood vessel.

Also under this rejection, at pages 12-14 of the Office Action, the Examiner asserts that small animal models of intimal hyperplasia disease and treatment are not predictive of success in other animals, particularly humans. Applicants respectfully maintain that small animal models are predictive of success in other animals, including humans. Applicants assert that for studies directed to treatment of blood vessels in mammals, the rabbit animal model is, and has been, accepted in the art and has been used extensively in studies reported in the scientific literature. The Strauss *et al.* (*Int. J. Radiation Oncology Biol. Phys.*, 2002, Vol. 54, No. 2) and Farb *et al.* (*Circulation*, 2001, Vol. 103) references were submitted to show that the rabbit is a suitable animal model and is still being used in studies for testing suitability of procedures in humans. If the rabbit model was not a valid model for procedures in humans, Applicants respectfully assert that clinical researchers would

not use it for their studies and it is unlikely that studies using rabbits would continue to be published in the scientific literature. While there may be some agents or methods unrelated to the subject invention that may have worked in rabbit models that subsequently may not have successfully transferred when attempted in humans, this does not exclude the rabbit model as a valid and useful animal model for human studies. Applicants maintain that the fact that the rabbit model has been used in the past and continues to be used in current scientific studies is evidence that the rabbit was, and remains, a valid model for other mammals, including humans. Applicants have also shown that the claimed method works on pig blood vessels.

Applicants would also bring to the Examiner's attention that they have received approval from the U.S. Food & Drug Administration (FDA) to initiate human clinical trials of the subject invention, as evidenced by the letters attached herewith. Specifically, Applicants have attached with this Amendment a letter dated July 16, 2003 by Dr. Joyce Frey of the FDA to Dr. James Parker of Ark Therapeutics Ltd. (the assignee of record of the subject application) indicating that Ark Therapeutics' Investigational New Drug (IND) application ("Adenovirus Vector (Ad-VEGF-D, Cobra-Bio Manufacturing) Expressing Human Vascular Endothelial Growth Factor D Gene; Delivered via Collagen Collar Device") may proceed to human clinical trials (although the July 16, 2003 letter references IND application No. 1010 (a typographical error), the correct IND application No. is 11010). Also included with this Amendment is a portion of Applicants' IND application, which sets forth the Introductory Statement and General Investigational Plan of the IND. The IND application was initially placed on clinical hold as indicated in an FDA letter of May 30, 2003 from Dr. Frey (a copy of which is attached with this Amendment) until certain issues were resolved to the satisfaction of the FDA. Those issues were subsequently satisfactorily resolved and the FDA allowed human clinical trials to be initiated (Dr. Frey in her July 16, 2003 letter states: "The clinical hold has been removed and your proposed study may proceed.").

The Manual of Patent Examining Procedure (MPEP) at §2107.03 clearly states:

> Thus, as a general rule, if an applicant has initiated human clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility. (emphasis in original).

It is clear from decisional caselaw, and the Patent Office's own rules, that the bar for therapeutic enablement and utility is not higher than the FDA requirements. Applicants have established therapeutic efficacy of the claimed method in rabbits and pigs, and based on the results in these animal models, the FDA has approved clinical trials on humans. In contrast, the Patent Office has, based on the same animal models, maintained that the claimed method is not enabled for animals other than rabbits. In view of Applicants' approval from the FDA to initiate human clinical trials, the Patent Office's own rules state that it is to be presumed that the subject matter of the trials has therapeutic utility in humans. Accordingly, Applicants respectfully assert that the claimed method meets the utility and enablement requirements of the patent statute.

In another aspect of this rejection, the Examiner asserts that the subject specification does not enable the use of any agonists of a Flt-1 or Flk-1/KDR receptor to which VEGF binds except for VEGF. Applicants respectfully assert that the subject specification enables the claimed method using agonists other than VEGF. However, by this Amendment, Applicants have amended claim 1 to recite that the agonist is a human VEGF protein (as previously recited in claim 7, now canceled by this Amendment).

In view of the above, reconsideration and withdrawal of the rejection under 35 USC §112, first paragraph, is respectfully requested.

Claims 1-9 are rejected under 35 USC §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. Under this rejection, the Examiner asserts that the written description of the subject application does not provide support for a genus of agonists of Flt-1 and Flk-1/KDR receptors. Applicants respectfully assert that there is adequate written description in the subject specification to convey to the ordinarily skilled artisan that they had possession of the claimed invention. However, as noted herein, Applicants have amended claim 1 to recite that the agonist is a human VEGF protein. Extensive written description for human VEGF protein can be found throughout the subject specification including, for example, at page 7, line 20, of the specification. Accordingly, reconsideration and withdrawal of the rejection under 35 USC §112, first paragraph, is respectfully requested.

Claims 1-6 and 9 are rejected under 35 USC §102(a) as anticipated by Laitinen *et al.* (1996). In addition, claims 1, 7, and 8 are rejected under 35 USC §103(a) as obvious over Laitinen *et al.* (1996) in view of Janjic *et al.* (U.S. Patent No. 5,859,228). Under both of these rejections, the Examiner indicates that the Laitinen *et al.* reference teaches inhibition of intimal proliferation in a rabbit artery *in vivo* by periadventitial delivery of a nucleic acid encoding VEGF and that the artery was not denuded of its epithelium. Applicants respectfully traverse these rejections.

While Applicants assert that the Laitinen *et al.* reference does not anticipate or render obvious the claimed invention, Applicants also respectfully assert that the Laitinen *et al.* reference (which is an abstract for the American Heart Association's annual conference in 1996) was not available to the public prior to the date of the conference: November 11-14, 1996. Attached with this Amendment is a copy of a letter dated May 22, 2002 from a representative of the American Heart Association submitted to the European Patent Office during prosecution of Applicants' European patent application corresponding to the subject application. The American Heart Association representative confirms in his letter that the abstracts for the 1996 American Heart Association annual conference were not available to the public until the date of the conference itself, which, as noted above, took place on November 11-14, 1996. Thus, the Laitinen *et al.* (1996) reference was published no earlier than November 11, 1996. As the Examiner is aware, the subject application claims foreign priority under 35 USC §119 to British priority application No. 9622852.3 filed November 1, 1996. The Examiner acknowledges Applicants' claim of foreign priority for the subject application and receipt of all priority documents on the Summary page of the Office Action dated November 16, 2001. Applicants respectfully assert that the claims pending in the subject application all find support in British priority application 9622852.3 and, therefore, are all entitled to the November 1, 1996 filing date of the British application. Thus, the Laitinen *et al.* (1996) reference is not effective prior art against the subject application. Accordingly, reconsideration and withdrawal of the rejections under 35 USC §102(a) and 35 USC §103(a) based on the Laitinen *et al.* (1996) reference is respectfully requested.

Claims 1-9 are rejected under 35 USC §103(a) as obvious over Asahara *et al.* (1996) in view of Mayberg (U.S. Patent No. 6,326,017), Goldstein *et al.* (U.S. Patent No. 5,962,427), and Gilbert *et al.* (1989). Claim 8 is also rejected under 35 USC §103(a) as obvious over Asahara *et al.* (1996) in

view of Mayberg (U.S. Patent No. 6,326,017) and Gilbert *et al.* (1989) and further in view of Janjic *et al.* (U.S. Patent No. 5,859,228). The Examiner asserts that Asahara *et al.* reference teaches that intimal hyperplasia in rabbits can be inhibited by delivering to an injured artery a plasmid encoding human VEGF 165. The Examiner states that the Mayberg patent teaches methods for localized delivery of agents to arteries. The Examiner further states that the Goldstein *et al.* reference teaches PLGA compositions for the controlled release of nucleic acids into cells *in vivo*. In addition, the Examiner states that Goldstein *et al.* teaches a rabbit model of intimal hyperplasia induced by surgical anastomosis. Applicants respectfully traverse these rejections.

Applicants respectfully assert that the claimed invention is not obvious over the cited references, regardless of whether the references are taken alone or in combination. However, Applicants also note that the primary reference cited in the rejections, Asahara *et al.* (1996), was published after the filing date of Applicants' British priority application No. 9622852.3. The Asahara *et al.* reference was apparently published in December 1996. As noted above, the claims pending in the subject application all find support in the British priority application and, therefore, are all entitled to the November 1, 1996 filing date of British priority application No. 9622852.3. Thus, the Asahara *et al.* (1996) reference is not effective prior art against the subject application. In the absence of the primary reference, the obviousness rejections cannot stand. Accordingly, reconsideration and withdrawal of the rejections under 35 USC §103(a) is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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DRP/sl

Attachments: copy of the letter dated May 22, 2002 from Richard L. Luna of the American Heart Association submitted to the EPO in the corresponding European patent application; copy of FDA IND application letter of May 30, 2003 by Dr. Joyce Frey to Dr. James Parker of Ark Therapeutics Ltd.; copy of FDA IND application letter dated July 16, 2003 by Dr. Joyce Frey to Dr. James Parker of Ark Therapeutics Ltd.; portion of the IND application No. 11010.